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CLINICAL TESTING OF ANTIMALARIALS BY I.G. FARBEN, ELBERFELD

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COMBINED INTELLIGENCE OBJECTIVES
SUB-COMMITTEE

C O N F I D E N T I A L

CLINICAL TESTING OF ANTIMALARIALS BY I.G. FARBEN, ELBERFELD, GERMANY.

Reported by

Lt. Col. HAMILTON SOUTHWORTH, U.S.P.H.S.

C.I.O.S. Target Number 24/3
Medical

COMBINED INTELLIGENCE OBJECTIVES SUB-COMMITTEE.
G-2 Division, SHAEF (Rear) APO 413.

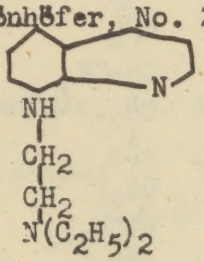
C O N F I D E N T I A L

T A B L E O F C O N T E N T S

Introduction.

The following is a literal translation of a report prepared by Drs. Schönhöfer and Kikuth of I.G. Farben, Elberfeld and delivered to Lt.Col. Hamilton Southworth on 25 May 1945. Schönhöfer affirms that the report covers all of the antimalarials, except Atebrin, Dimeplasmin and Diapromin, manufactured by I.G. Farben since 1924 which had been subjected to clinical tests. The three exceptions are covered in other reports.

APROCHIN (Dr. Schönhöfer, No. 287, 15 July 1924).



Tablets 0.1 gm. in form of the dihydrochloride.

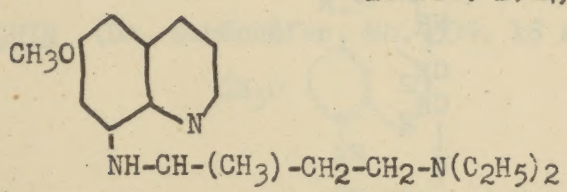
Bird toxicity	Effect
1/200	1/1600

In comparison to this, quinine -

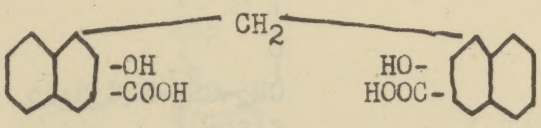
1/200	1/800

Aprochin was tested by Prof. Sioli, Düsseldorf, in inoculation malaria of paralytic patients, in 1924; it was found to be ineffective. Methemoglobin appeared as a pronounced concomitant effect.

BEPROCHIN = PLASMOCHIN (Dr. Schönhöfer, No. 335, 16 Dec. 1924).



Capsules (because hygroscopic) @ 0.01 gm. of the dihydrochloride, later tablets of the methane salt.

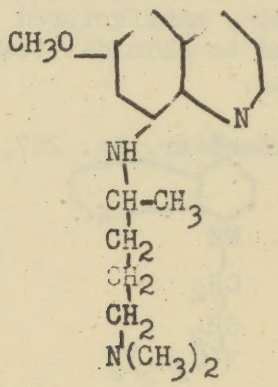


tablets @ 0.01 gm. calculated on basis of monohydrochloride.

Toxicity	Effect
1/800 - 1/1600	1/15000

Clinically tested first by Prof. Sioli, Düsseldorf, in inoculation malaria, with good effect; then by Prof. Mühlens, Hamburger Tropeninstitut, where effect upon natural malaria was confirmed; then by Dr. Höhl, in Spain, who first discovered there the gamete effect.

CEPROCHIN (Dr. Schönhöfer, No. 336, 7 Jan 1925).

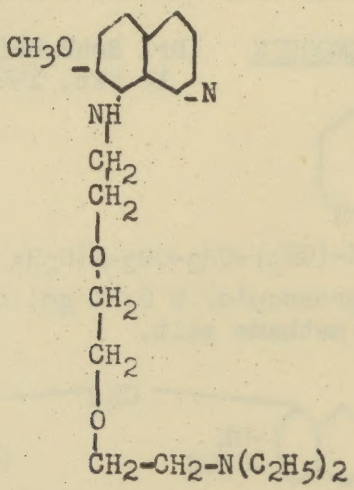


Tablets @ 0.01 gm. in form of the methane salt, calculated on basis of the monohydrochloride.

Toxicity	Effect
1/800	1/24000

Because the preparation of the substance is much cheaper, it was hoped that it could replace plasmochin which is more expensive. The substance was tested in the Hamburger Tropeninstitut in natural malaria; its effect was approximately that of plasmochin, but its toxicity was greated (considerable injury to the opticus).

DEPROCHIN (Dr. Schönhofer, No. 357, 4 March 1925).

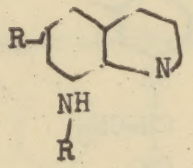


Methane salt @ 0.01 gm. calculated on basis of monohydrochloride.

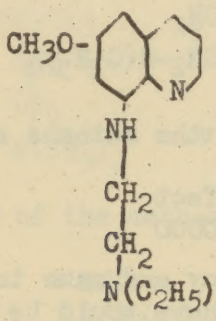
Toxicity	Effect
1/400	1/25000

Tested by Prof. Sioli, Düsseldorf, in inoculation malaria, it showed the same effect as plasmochin, in spite of its lower toxicity. As preparation of this substances was very expensive, no further clinical tests were performed.

Translators Note: It is believed that the formula should be



EPROCHIN (Dr. Schönhöder, No. 313, 3 Nov. 1924).

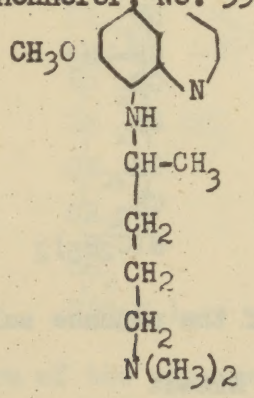


Tablets @ 0.01 gm of the dihydrochloride.

Toxicity	Effect
1/800	1/1200

In spite of a less favorable index than in the case of plasmochin, this preparation was tested on inoculation malaria by Prof. Sioli, Düsseldorf, because it was manufactured very cheaply. The effect, h however, was unsatisfactory.

GEPROCHIN (Dr. Schönhöfer, No. 339, 18 Aug. 1925).

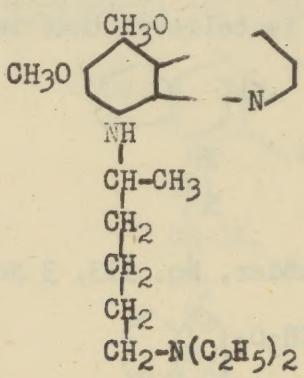


Tablets @ 0.01 gm of the methane salt, calculated on the basis of the monohydrochloride.

Toxicity	Effect
1/800	1/50000

Prof. Sioli, Düsseldorf, tested this preparation on inoculation malaria and found no advantages over plasmochin. No further tests.

HAPROCHIN (Dr. Schönhöfer, No. 810, 8 Aug. 1929).

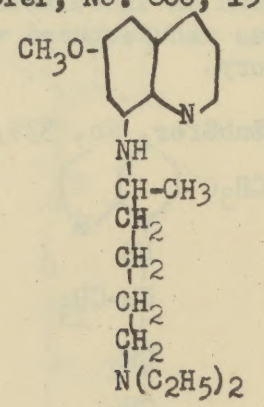


Tablets @ 0.01 gm. in form of vthe methane salt, calculated on the base.

Toxicity	Effect
1/1500	1/100000

On basis of the higher efficacy and same toxicity as those of plasmochin it was expected that there would be an especially favorable effect also upon human malaria. Prof. Sioli, Düsseldorf, tested the substance in inoculation malaria and was able to find a slight superiority over plasmochin; the same superiority was also determined by Prof. Mühlens, Hamburg, in natural malaria. However, the advantage was too slight to begin commercial production of the substance.

IPROCHIN (Dr. Schönhöfer, No. 800, 15 June 1929).

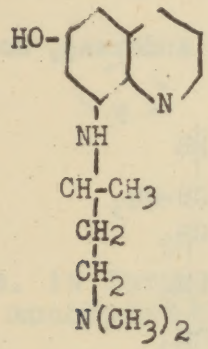


Tablets @ 0.01 gm. in form of the methane salt, calculated as a base.

Toxicity	Effect
1/1500	1/100000

For the canary, toxicity and effect were the same as those of plasmochin; but in the Halteridium infection of the rice finches its effect was twice as high. For this reason the gametocidal effect in natural malaria was to be examined. It was tested by Prof. Sioli, Düsseldorf, and in the Hamburger Tropeninstitut. No superiority to plasmochin could be found.

OPROCHIN - CERTUNA (Dr. Schönhöfer, No. 417, 30 Nov. 1925).

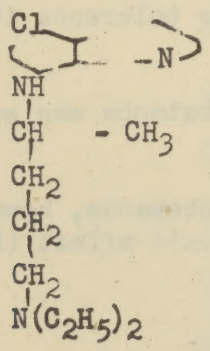


Tablets @ 0.01 gm. in form of the methane salt, calculated as a base.

Toxicity	Effect
1/400	1/25000

The substance was fiest examined by Prof. Sioli, Düsseldorf, in inoculation malaria because of its low toxicity (very slight formation of methemoglobin), and the expected effect and low toxicity were confirmed. The tests were discontinued for a long period because of the difficulty of preparing the substance. Later, on the basis of works by Missiroli, etc., it was introduced commercially, since in the meantime a new method of preparation has been found.

ELPROCHIN - MEROCHIN (Dr. Schönhöfer, No. 836, 1 Jan 1929).

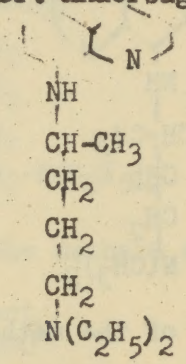


Tablets @ 0.01 gm. in form of the methane salt, calculated on the basis of monohydrochloride.

Toxicity	Effect
1/800	1/6000

This preparation is the first one of the plasmochin series which has no effect upon the Halteridium of the rice finch, and thus must be considereed similar to quinine, Thus an atabrine effect was expected. Prof. Sioli, Düsseldorf, confirmed the effect in inoculation malaria. Dr. A. Eckhardt, Tanganyika Territory, tested it only with isolated tropical malaria patients; a certain effect was established, but further testing was not performed because of the toxicity of the substance.

UPROCHIN = ANTIPLASMIN (Dr. Andersag, No. 227, 20 April 1931).



Tablets @ 0.01 gm. in form of the methane salt, calculated on basis of monohydrochloride.

Toxicity	Effect
1/800	1/12000

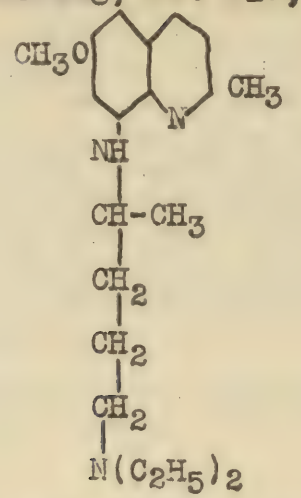
On basis of the chemotherapeutic tests uprochin proved inferior to plasmochin in Roehl's test in bird malaria; but in the Halteridium infection the substance showed a better effect.

On basis of this fact it was hoped that uprochin should, in principle, be equally effective toward human malaria as plasmochin, and if possible, with better tolerance it might have a more pronounced gamete effect.

On 16 Jan. 1932 the substance was sent to Col. James with the name "Antiplasmin".

In human malaria the substance, however, proved unusable because of its unexpectedly high toxic effect (febrifacient); it was thus turned down by Col. James.

ANDRACHIN (Dr. Andersag, No. 513, 12 Sept 1933).

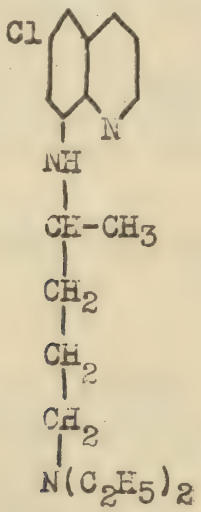


Tablets @ 0.1 gm. in form of the methane salt, calculated on basis of the monohydrochloride.

Toxicity	Effect
1/1500	1/100000

This substance displayed double efficacy in Halteridium infection of the rice finch (gamete effect). It was tested by Prof. Bastianelli (Rome?) who, in natural malaria, was unable to find an effect that was superior to that of plasmochin.

CHINALON (Dr. Andersag, No. 309, 2 Nov 1931).

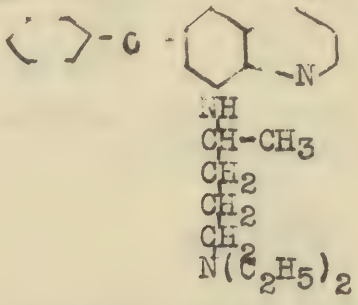


Tablets @ 0.01 gm. in form of the methane salt, calculated on basis of monohydrochloride.

Toxicity: 1/800 Effect: 1/6000

Since this substance displayed only a very slight effect upon bird malaria, but a very strong effect upon the Halteridium infection of the rice finch, it was tested for its specific gametocidal effect upon the crescents of tropical malaria. After a preliminary test by Prof. Sioli, Düsseldorf, who determined a weak effect upon inoculation malaria, it was tested in Tanganyika Territory in tropical malaria and a pronounced effect upon the crescents of this infection was found. There was, however, no economic interest in a new preparation of this substance, since no advantages were determined over those of plasmochin.

PHENOCHIN (Dr. Andersag, No. 215, 25 March 1931)

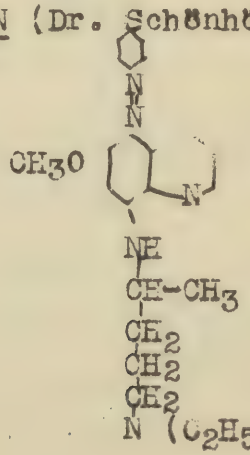


Tablets @ 0.01 gm. in form of the methane salt, calculated on basis of monohydrochloride.

Toxicity	Effect	Halteridium Effect
1/800	/ ∅	1/12000

This substance has no effect at all upon bird malaria, but upon the Halteridium infection of the rice finch. Thus it was expected to be a pronounced gameticide in human malaria. The substance was tested by Col. James 10 July 1932. He found that it was surprisingly well tolerated in comparison to animal tests, and he was able to determine a gametocidal effect.

RHODOCHIN (Dr. Schönhöfer, No. 675, 13 August 1928)

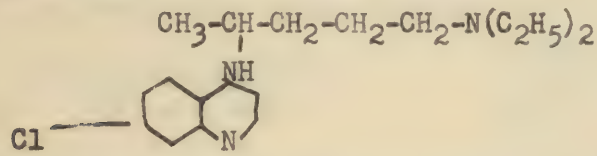


Tablets @ 0.1 gm. in form of the methane salt, equal to 0.05 Rhodochin base.

Toxicity	Effect
1/100	1/12000

Of all plasmochin derivatives, rhodochin displays the greatest index. Thus in clinical tests it was expected that a special effect would be attained by higher dosage. It was tested in Tanganyika Territory in tropical malaria and found to be equivalent to plasmochin. Tests in the Hamburger Tropeninstitut (Prof. Giemsa) yielded the same results.

RESOCHIN (Dr. Andersag, No. 564).

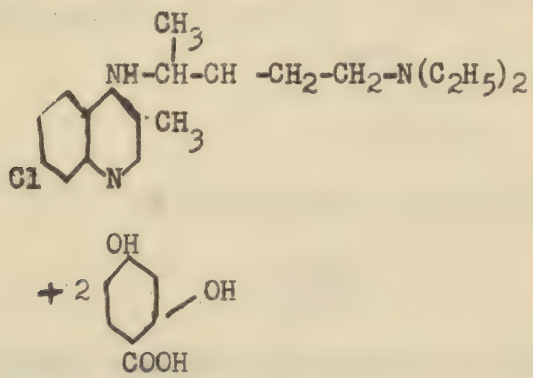


Tablets @ 0.1 gm. form of the B-resorcyl-acidic salt.

Tixicity 1/300 Effect 1/3000 No effect upon Halteridium infection.

Since here, an atabrine-like effect was to be expected, the substance was tested by Prof. Sioli, Düsseldorf, in inoculation malaria. The toxicity of this substance wash, however, so great in comparison to its effect, that it was treated no further.

SONTOCHIN R (Dr. Andersag,No. 751, 20 May 1937)
(Dr. Breitner, No. 141, 22 June 1937).



Tablets @ 0.1 gm. in form of the B-resorcin-acidic salt calculated as base.

Toxicity	Effect
1/100	1/1500

Since thiw substance revealed a much lower toxicity than resochin it was given to Prof. Sioli for testing in inoculation malaria; he confirmed its good effect and low toxicity; Prof. Mühlens tested it in natural malaria and obtained the same results.

SONTOCHIN M is the methane salt of the Sontochin base.

Tablets @ 0.1 gm. calculated according to the base. Since the tablets do not have a bitter taste, they were tested for their resorption effect toward malaria. The same effect was found as that of Sontochin R. Further tests by Decourt in Morocco, etc.

SONTOCHIN C is the dihydrochloride of the Sontochin base.

Dragées @ 0.1 gm. calculated according to the base. Ampules of 2 cc. of a 5 percent solution = 0.1 gm. (calculated according to the base.).

SONTOCHIN I is an isomere mixture of the 7-chloroquinoline-derivative (60%) and the 5-Chloroquinoline-derative (50%). *
Tablets @ 0.1 gm. in form of the methane salt, calculated as a base.

Toxicity	Effect
1/100	1/15000

(* Translatory Note: 60% plus 50% = 110%)

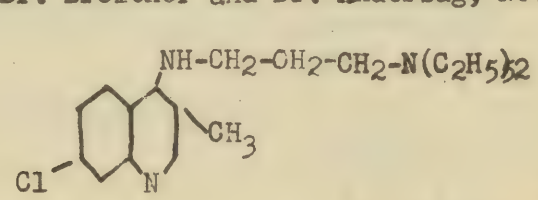
Prof. Sioli, Düsseldorf, found in inoculation malaria the same effect as with Sontochin M (December 1938).

SONTOCHIN U is the 5-chloroquinoline-derivative.

Toxicity	Effect
1/100	ø

Tablets @ 0.1 gm. in form of the dihydrochloride calculated as a base. Prof. Sioli found no effect upon inoculation malaria.

BRACHYSAN (Dr. Breitner and Dr. Andersag, No. 927, 19 Oct. 1939).



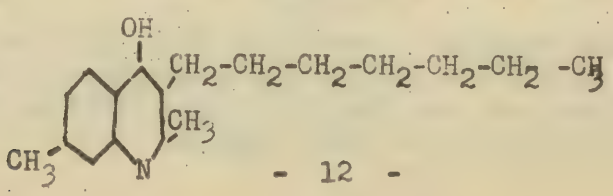
x 2HCl

Tablets @ 0.1 gm. of the dihydrochloride.

Toxicity	Effect
1/100	1/1500

Since this substance is produced at lower expense than Sontochin, it was examined by Prof. Sioli in inoculation malaria. He found the same results as with Sontochin.

ENDOCHIN (Dr. Salzer, No. 265, 3 Oct. 1940).



Tablet @ 0.1 gm.

Toxicity	Effect	Halteridium Effect
1/25	.1/3000	1/200

In bird malaria this substance showed for the first time a causal prophylactic effect. Prof. Sioli examined first the malaria effect upon inoculation malaria, and then he tested the prophylactic effect on malarial paralytics via mosquito infection. He was unable to find an effect in inoculation malaria, nor in mosquito-transmitted malaria infection.

I.G. Farbenindustrie Aktiengesellschaft
Werk Elberfeld.

/s/ Dr. Schönhöfer pp. Kikuth

ELB. 20 May 45.